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**Filed** : **October 10, 2000**

### **REMARKS**

Claims 1, 2, 4, 5, 8-11, 29, 36-38, 40-42, 47, 51, 53, 56, and 58 have been amended and Claims 6, 12, 13, 27, 57, and 59 have been cancelled without prejudice. As a result, Claims 1-5, 7-11, 29, 36-42, 44, 47-51, 53, 56, and 58 remain pending in the present application. Support for the amendments is found in the specification and claims as filed. Accordingly, the amendments do not constitute the addition of new matter.

Applicants would like to initially thank Examiner Rawlings for the courteous interview extended to Applicants' representatives, Daniel Altman and Connie Tong, on May 12, 2005. Applicants have amended the claims along the lines discussed during the interview. On the basis of the interview, and in response to the Office Action mailed December 7, 2004, Applicants respectfully request the Examiner to reconsider the above-captioned application in view of the foregoing amendments and the following comments.

#### Objection of the Specification

The substitute specification sent with the previous Amendment was not entered because the marked-up copy of the substitute specification failed to show each and every change made relative to the immediate version of the specification. The present objections to the specification are the result of the non-entry of the substitute specification of July 30, 2004.

The specification has been amended to include the changes already made to the originally filed specification by the amendment filed November 6, 2003. The present amendments to the specification are made in response to the objections to the specification as outlined in the present Office Action and to reflect amended sequence identifiers. These amendments include amending the Abstract to be one paragraph; insertion of sequence identifiers; demarcation of trademarked terms; and, correction of various misspellings. Additionally, the misspelling in Figure 2 has been corrected in response to the drawing objection. No new matter has been added.

Accordingly, Applicants respectfully request the Examiner to reconsider and enter the present substitute specification.

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Objection to Claims

The Examiner objected to Claim 2 because of a mismatched sequence. The mismatched sequence has been corrected. A replacement sequence listing reflects the corrected SEQ ID NO:2, which corresponds to the sequence in Figure 2. Also, the sequence in Figure 2 is now correctly labeled "pMSF-1 $\alpha$ ."

The Examiner objected to Claim 27 for a misspelling of "SEQ ID NO." Claim 27 has been cancelled without prejudice.

The Examiner objected to Claim 29 because of improper Markush claim language. Claim 29 has been amended to correct the Markush claim language.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the claim objections.

Rejection under 35 U.S.C. § 101

The Examiner rejected Claim 8 under 35 U.S.C. § 101 because the Examiner believes that the claimed invention is directed to non-statutory subject matter. Claim 8 has been amended to recite "isolated" before "host cell," as suggested by the Examiner.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. § 101.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected Claims 1-3, 6-13, 27, 29, 56, 57, and 59 under 35 U.S.C. § 112, first paragraph, as failing to comply with either the written description requirement or the enablement requirement. The Examiner is objecting to the terms "variants thereof," "fragments thereof," and "derivatives." The Examiner believes that these terms describe an abundance of different proteins, which differ in structure and function. Claim 1 has been amended to remove reference to the variants, fragments, and derivatives. The specification describes a number of utilities for the polynucleotide recited in Claim 1. For example, the polynucleotide can encode a polypeptide having MSF activity (See page 46 of the substitute

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specification). It can also encode a protein that can be used to raise antibodies unique to the MSF tail (see page 46 of the substitute specification) and to hybridize to a gene that encodes MSF activity, such as to obtain information regarding the MSF gene by using PCR reactions (see page 47 of the substitute specification).

Claim 10 has been amended to recite “[a] polypeptide encoded by the polynucleotide having SEQ ID NO: 4,” as suggested by the Examiner during the interview. This amendment also removes reference to various fragments and derivatives, thereby overcoming the rejection.

The Examiner rejected Claims 6, 13, and 59 under 35 U.S.C. § 112, first paragraph, for written description and under 35 U.S.C. § 112, second paragraph, for the term “migration stimulation factor activity.” These claims have now been cancelled, rendering the rejection moot.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejections under 35 U.S.C. § 112, first paragraph.

#### Rejection under § 102-Grey and Schor

The Examiner rejected Claims 10-13, 27, 29, 56, 57, and 59 under 35 U.S.C. § 102(b) as being anticipated by Grey et al. (*PNAS* 1989 Apr; 86: 2438-2442), as evidenced by Schor et al. (*Cancer Res* 2003 Dec; (24): 8827-8836).

Grey et al. describes the purification of the migration stimulating factor produced by fetal and cancer patient fibroblasts, but no amino acid sequence information is given. Although the Schor et al. reference is not prior art, the Examiner uses the reference to show that the polypeptide in the Grey et al. reference inherently has the recited sequence. However, in order to inherently anticipate, there must be “a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.” M.P.E.P. 2112, (emphasis in original citation). “The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.” *Id.*

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In the present case, no evidence is present that the Grey et al. reference necessarily discloses a protein having the recited sequence. Grey et al. does not say which portion of the protein is obtained. Nor does it disclose the sequence of the portion that was obtained. We now know that there are at least two forms of MSF. The present specification discloses that there is a 642-amino acid form. Schor et al. discloses a 657-amino acid form. Attached, as an appendix, is the entry for European Molecular Biology Laboratory accession number AJ535086, the sequence for the full length cDNA cloned in the Schor et al. reference; see page 8829, results section. The translation of the cDNA is shown in the entry and is different from the claimed sequences. The protein translation of the cDNA of accession number AJ535086 shows a 657-residue protein. The sequence as shown in Figure 2 contains 642 residues. The sequence as shown in Figure 2 does not contain a 15-residue portion that is present in accession number AJ535086.

Thus, the sequence in Figure 2 is not the same as the sequence in Schor et al. There is no way to know whether the peptide in Grey et al. has the same sequence as the one disclosed in the present application. There is no sequence information or any other identifying information about the sequence in Grey et al that would lead one in the art to conclude that the Grey et al. peptide is the same as the peptide disclosed in the present application. Accordingly, Claim 10, which recites a sequence based on Figure 2, must be considered novel over Grey et al.

Claim 10 has been amended to recite “[a] polypeptide encoded by the polynucleotide having SEQ ID NO: 4.” Claim 5, which is directed to the polynucleotide having SEQ ID NO: 4, has been found allowable. Accordingly, a polypeptide based on the polynucleotide having SEQ ID NO: 4 should also be allowable. Essentially, a polypeptide is a product of the translation process. Therefore, a translation of the patentable polynucleotide having SEQ ID NO: 4 should also provide for a patentable polypeptide sequence.

The features of Claims 29 and 56 are not inherent in Grey et al. Claim 29 is directed to specific fragments found in MSF. Claim 56 is directed to a pharmaceutical composition comprising a polypeptide of Claim 10, which is based on SEQ ID NO:4.

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Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. § 102(b) with respect to Grey and Schor.

Rejection under § 102-WO 94/16085 A2

The Examiner rejected Claims 1-3, 6-13, 27, 56, and 59 under 35 U.S.C. § 102(b) as being anticipated by WO 94/16085 A2. According to the Examiner, WO 94/16085 A2 discloses a polypeptide comprising a variant of SEQ ID NO:1.

According to M.P.E.P. 2131.01, "a claim is anticipated only if each and every element as set forth in the claims is found, in either expressly or inherently described, in a single prior art reference."

Claim 1 has been amended to recite "A recombinant polynucleotide encoding a polypeptide comprising the amino acid sequence VSIPPRNLGY (SEQ ID NO: 41): wherein the polypeptide has migration stimulation factor activity; and wherein migration stimulation factor activity refers to stimulation of adult skin fibroblast migration."

VSIPPRNLGY (SEQ ID NO: 41) is unique to MSF. See Example 3 on page 46 of the specification. WO 94/16085 A2 relates to polypeptides that comprise sequences derived from fibronectin. WO 94/16085 A2 does not disclose a polypeptide comprising a variant of SEQ ID NO:41.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. § 102(b) with respect to WO 94/16085 A2.

Rejection under § 102-Bristow and Benoliel

The Examiner rejected Claims 12, 56, 57, and 59 under 35 U.S.C. § 102 (b) as being anticipated by Bristow (*Trends Biotechnol.* 1993 Jul; 11 (7): 301-305), as evidenced by Benoliel et al. (*J. Cell Sci.* 1997 Sep; 110 (pt 17):2089-2097. Bristow et al. discloses recombinant-DNA-derived insulin analogues as potentially useful therapeutic agents. Benoliel et al. discloses that insulin stimulates haptotactic migration of human epidermal keratinocytes through activation of NF-κB transcription factor.

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According to the Examiner, Claims 12, 56, 57, and 59 read on any polypeptide that could be produced by a process comprising culturing a host cell according to Claim 8.

Claims 12, 57, and 59 have been cancelled without prejudice.

Claim 56 has been amended to be an independent claim and recites: “[a] pharmaceutical composition comprising a polypeptide according to Claim 10 and a pharmaceutically acceptable carrier.” Claim 10 recites a polypeptide encoded by the polynucleotide having SEQ ID NO:4.

Nothing in the prior art discloses or suggests either the polypeptide encoded by a polynucleotide having SEQ ID NO:4 or the inclusion of such a polypeptide in a pharmaceutically acceptable carrier.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. § 102(b) with respect to Bristow and Benoliel.

#### Rejections under § 103

The Examiner rejected Claims 1-3 and 6-9 under 35 U.S.C. § 103(a) as being unpatentable over Grey et al. (*PNAS* 1989Apr; 86: 2438-2442), as evidenced by Schor et al. (*Cancer Res.* 2003 Dec; 63 (24): 8827-8836), in view of Bendig (*Genet. Eng.* 1988; (7): 91-127).

As stated above, Grey et al. describes the purification of the migration stimulating factor produced by fetal and cancer patient fibroblasts, but no amino acid sequence information is given. Grey et al. utilized fibroblast cell lines from foreskin, fetal limb dermal fibroblasts, and forearm dermal fibroblasts from cancer patient. Although the Schor et al. reference is not prior art, the Examiner uses the reference to show that the polypeptide in the Grey et al. reference inherently has the recited sequence. Schor et al. utilizes a human fetal lung fibroblast cell line. Accordingly, Schor et al. uses a different source for characterization of the polypeptide than Grey et al.

Attached, as an appendix, is the entry for European Molecular Biology Laboratory accession number AJ535086, the sequence for the full length cDNA cloned in the Schor et al. reference; see page 8829, results section. The translation of the cDNA is shown in the entry

and is different from the claimed sequences. The protein translation of the cDNA of accession number AJ535086 shows a 657-residue protein. The sequence as shown in Figure 2, contains 642 residues. The sequence as shown in Figure 2 also does not contain a 15-residue portion that is present in accession number AJ535086. Accordingly, the sequence as shown in Figure 2 is different from the sequence in Schor et al.

Claim 1 has been amended to recite "A recombinant polynucleotide encoding a polypeptide comprising the amino acid sequence VSIPPRNLGY (SEQ ID NO: 41): wherein the polypeptide has migration stimulation factor activity; and wherein migration stimulation factor activity refers to stimulation of adult skin fibroblast migration." SEQ ID NO:41 comprises a unique tail of MSF.

Grey et al. does not teach or suggest a recombinant polynucleotide encoding a polypeptide comprising the amino acid sequence (SEQ ID NO: 41). Grey et al. does not provide any polynucleotide or polypeptide sequences. While the Examiner uses the non-prior art Schor et al. reference to show that the polypeptide in the Grey et al. reference inherently has the recited sequence, Schor et al. utilizes a different source as Grey et al. to obtain the polypeptide. Schor et al. does not prove what Grey et al. obtained. Even if Schor et al. did prove so, the polynucleotide sequence is not suggestive. Accordingly, the polypeptide in Schor et al. is not necessarily representative of the polypeptide in Grey et al.

Moreover, according to M.P.E.P. 2144.09, "the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs." See *In re Deuel*, 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995). There is no prior art cited that specifically suggest the claimed DNA. Therefore, the use of the Bendig reference is irrelevant to the present rejection.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

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Rejoinder

According to M.P.E.P. 821.04, where product and process claims drawn to independent and distinct inventions are presented in the same application, applicant may be called upon under 35 U.S.C. § 121 to elect claims to either the product or process. The claims to the nonelected invention will be withdrawn from further consideration under 37 C.F.R. § 1.142. However, if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined. Accordingly, upon allowance of Claims 1 and/or 10, the Applicants request rejoinder of Claims 36-42, 44, 47-51, 53, and 58, in accordance with M.P.E.P. 821.04.

Replacement Sequence Listing

Enclosed herewith are (1) a paper copy of the Replacement Sequence Listing, and (2) a computer-readable version of the Replacement Sequence Listing. This Amendment directs entry of the paper copy of the Listing into the application. No new matter is being added herewith.

Verification under 37 C.F.R. § 1.821(f) & (g)

All of the sequences in the attached Sequence Listing were included in the application as filed. Pursuant to 37 C.F.R. § 1.821(g), no new matter is being added herewith. As required under 37 C.F.R. § 1.821(f), I hereby verify that the data on the enclosed disk and the paper copies of the Sequence Listing are identical.

CONCLUSION

In view of the foregoing amendments and comments, it is respectfully submitted that the present application is fully in condition for allowance, and such action is earnestly solicited.




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The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully invited to call the undersigned in order to resolve such issue promptly.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: August 18, 2005

By:   
Connie C. Tong  
Registration No. 52,292  
Agent of Record  
Customer No. 20,995  
(949) 760-0404

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## **SUMMARY OF INTERVIEW**

### Identification of Claims Discussed

All the pending claims were discussed with respect to issues relating to 35 U.S.C. §§ 112, 102, and 103. In particular, claim language of Claims 1 and 10 were discussed. Claim 1 is directed to a polynucleotide. Claim 10 is directed to a polypeptide. The Examiner acknowledged that Claims 4 and 5 are allowed.

### Proposed Amendments and Principal Arguments

Applicants proposed amending Claim 1 to recite a portion of polynucleotide sequence that encodes a unique tail of MSF, namely "VSIPPRNLGY." This unique tail is believed to be patentable over the cited prior art. Applicants proposed removing the terms "variants thereof," "fragments thereof," and "derivatives" to overcome the rejections under 35 U.S.C. § 112, first paragraph.

Applicants proposed amending Claim 10 to recite a portion of the polypeptide sequence of SEQ ID NO.1 from residues 19-660. This portion is believed to be patentable over the cited prior art. As with Claim 1, Applicants proposed removing the terms "variants thereof," "fragments thereof," and "derivatives" to overcome the rejections under 35 U.S.C. § 112, first paragraph.

### Results of Interview

Applicants agreed to file an Amendment which would include the proposed amendments discussed during the interview.

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#### **AMENDMENTS TO THE DRAWINGS**

Figure 2 has been amended to correct the reference to pMSF-1 $\alpha$ . Figure 3 has been amended in accordance with the Replacement Sequence Listing. Clean copies of Figures 2 and 3 and redlined copies of Figures 2 and 3 are enclosed. Formal drawings will be submitted upon approval of the amendments of Figures 2 and 3.